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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/085,297	02/28/2002	Lars Karlsson	ORT-1597	8611

7590 11/19/2003

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EXAMINER	
FALK, ANNE MARIE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/085,297	KARLSSON ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *0202*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The preliminary amendment filed February 28, 2002 has been entered. Claims 1 and 2 have been cancelled. Claims 3-8 have been newly added.

Accordingly, Claims 3-8 are pending in the instant application.

Specification

The disclosure is objected to because of the following informalities:

At page 5, line 20, page 25, line 15, page 26, line 11, and page 27, line 14, text is missing. The sentences do not conclude with a period.

Appropriate correction is required.

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: Claim 7 recites microinjection of DNA into ES cells, but the specification fails to provide antecedent basis for this limitation.

The specification is objected to for referencing drawings that were not included in the application as-filed. The specification mentions Figures 8 and 9, but no such figures are present in the application. All references to Figures 8 and 9 must be omitted from the specification.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It does not state that the person making the oath or declaration has reviewed and understands the contents of the specification, including the claims, as amended by any amendment specifically referred to in the oath or declaration.

A preliminary amendment was filed on 3/27/02. However, the amendment is not specifically referred to in the declaration.

It does not identify the mailing address of each inventor. A mailing address is an address at which an inventor customarily receives his or her mail and may be either a home or business address. The mailing address should include the ZIP Code designation. The mailing address may be provided in an application data sheet or a supplemental oath or declaration. See 37 CFR 1.63(c) and 37 CFR 1.76.

The mailing address of Per Peterson has been omitted.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 3-8 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 3-8 of copending Application No. 10/109,165. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claims 3-8 of this application conflict with claims 3-8 of Application No. 10/109,165. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claim 7 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 7 is directed to the method of Claim 6 wherein the introducing of step (a) is by electroporation or microinjection.

The specification does not contemplate microinjection of DNA into ES cells. Applicants have not pointed to any support in the specification for this new claim limitation. At page 17 of the specification, transfection of ES cells by electroporation is described. However, nowhere does the

specification describe microinjection of DNA into ES cells. Typically, DNA is introduced into ES cells by electroporation because homologous recombination events are rare and selection from a large pool of transfected cells is required. To provide support for the claim limitation referring to microinjection of DNA into ES cells, the specification must specifically contemplate this methodology. The Examiner has reviewed the specification and does not find specific support for this claim limitation. Thus, the specification does not provide a written description for microinjection of DNA into ES cells.

Enablement

Claims 3, 4, 5, and 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse comprising within its genome a homozygous disruption in an endogenous H2-Oa gene, wherein disruption is generated by targeted replacement with a non-functional H2-Oa gene, and wherein said disruption results in said mouse having an increase in the amount of serumn IgG1 at 10 months of age as compared to wild-type H2-Oa mice and a cell isolated from said mouse, does not reasonably provide enablement for a transgenic mouse comprising within its genome a heterozygous disruption in its endogenous H2-Oa gene or a cell isolated from said mouse. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a transgenic mouse whose somatic and germ cells comprise a disruption in an endogenous H2-Oa gene, wherein disruption is generated by targeted replacement with a non-functional H2-Oa gene, and wherein said disruption results in said mouse having an increase in the amount of serum IgG1 at 10 months of age as compared to wild-type H2-Oa mice.

The specification fails to provide an enabling disclosure for a mouse comprising within its genome a heterozygous disruption in its endogenous H2-Oa gene because a heterozygous mouse would be substantially different structurally and biologically from a homozygous mouse, as the heterozygous

mouse would express the wild-type H2-Oa class II MHC molecule, whereas the homozygous mouse would not express any H2-Oa class II molecule at all. This would be expected to result in a substantially different phenotype for the heterozygous mouse as compared to the homozygous mouse. The instant specification teaches the phenotype of the homozygous mouse (pages 22-33), but does not teach the phenotype of the heterozygous mouse. Furthermore, the specification does not provide specific guidance for obtaining a heterozygous mouse that exhibits an increase in the amount of serum IgG1 at 10 months of age as compared to a wild-type H2-Oa mouse. Moreover, for the reasons discussed below, the phenotype of a knockout mouse is unpredictable.

The specification fails to provide an enabling disclosure for a heterozygous mouse of the type claimed, because the phenotype of a knockout animal is unpredictable and the specification does not teach the phenotype for anything other than the homozygous knockout mouse, nor does it teach how to prepare heterozygous mice that have the phenotype recited in the claims. The specification teaches only how to use transgenic mice having the disclosed transgene-dependent phenotypic alteration (i.e., increased serum IgG1). While gene knockout techniques are well-developed for the mouse, the phenotype of a knockout mouse is unpredictable. Moens et al. (1993) disclose that two mutations produced by homologous recombination in two different locations of the N-myc gene produce two different phenotypes in mouse embryonic stem cells, one leaky and one null. Jacks et al. (1992) demonstrated an unexpected phenotype in retinoblastoma (*Rb*) gene knockout mice. Tumors were found to arise not in the retinas, as found in humans, but rather in the pituitary gland. Furthermore, only the heterozygotes are viable. Another prime example of phenotypic differences in animals having the identical gene knocked out is the HPRT gene. HPRT-deficient mice are phenotypically normal, in contrast to patients with Lesch-Nyhan syndrome, a severe neurological condition caused by HPRT deficiency in humans. The widely varying phenotypes may be the result of differences in the purine metabolism between humans and mice (see Kuehn et al., 1987 and Jaenisch, 1988). Thus, the phenotype of a knockout mouse is unpredictable. Even differences

in the genetic background of transgenic mice can have an unpredictable effect on phenotype (Sigmund, 2000). Donehower et al. (1995) have studied the effects of genetic background on tumorigenesis in p53-deficient mice. In addition to finding that genetic background alters the spectrum of tumors that develop in p53-deficient mice, the authors also demonstrated that nullizygous mice make a good lymphoma model, whereas the heterozygous mice are useful as a model of Li-Fraumeni syndrome. The combined effect of gene disruption and genetic background cannot be predicted and therefore the phenotype of the heterozygous mouse as claimed has not been established. In the absence of specific guidance, the production of the desired transgene-dependent phenotypic alteration resulting from the disruption of an one allele of the H2-Oa gene as recited in the claim, is unpredictable. In the absence of specific guidance, the skilled artisan would not know how to use the full scope of the mice as claimed. Absent an appropriate phenotype, undue experimentation would have been required for the skilled artisan to determine how to use the heterozygous knockout mice in the same manner disclosed for the homozygous knockout mice. In view of the limited guidance in the specification, the limited working examples directed to characterizing the phenotype of the homozygous knockout mouse, the unpredictability of phenotypic alterations of knockout animals and the further unpredictability of the combined effect of gene disruption and genetic background, one skilled in the art would have been required to engage in undue experimentation in order to make and use the full scope of transgenic mice claimed.

In the absence of specific guidance, one skilled in the art would not know how to use a transgenic mouse that does not exhibit the specific knockout-dependent phenotype disclosed in the instant specification, without undue experimentation.

For the reasons discussed above, one of skill in the art would not be able to predict the phenotype of the heterozygous mouse, and therefore would not know how to use the heterozygous mouse.

Claims limited to (i) a transgenic mouse whose somatic cells and germ cells are **homozygous** for a disruption in an endogenous H2-Oa gene, wherein disruption is generated by targeted replacement with

a non-functional H2-Oa gene, and wherein said disruption results in said mouse having an increase in the amount of serum IgG1 at 10 months of age as compared to wild-type H2-Oa mice and (ii) cells isolated from said mouse, would be appropriate.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a step for selecting an embryonic stem cell having the desired genetic modification.

Claims 6 and 7 are indefinite in their recitation of "a selectable marker sequence" because it is unclear if the term is intended to refer to a selectable marker **gene** or if the nucleic acid sequence itself is intended to be the selectable marker.

Claim 8 is indefinite in its recitation of "derived from" because the nature and number of derivative processes is unclear or unknown. The term "derived from" can potentially include a very large number of undefined derivative processes. Thus, the meets and bounds of the claim are not clearly set forth. Use of the term "isolated from" would be remedial.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 3-8 are rejected under 35 U.S.C. 102(a) as being anticipated by Liljedahl et al. (Immunity (February 1, 1998) 8(2): 233-243).

The claims are directed to a transgenic mouse whose somatic and germ cells comprise a disruption in an endogenous H2-Oa gene, wherein disruption is generated by targeted replacement with a non-functional H2-Oa gene, and wherein said disruption results in said mouse having an increase in the amount of serum IgG1 at 10 months of age as compared to wild-type H2-Oa mice. The claims are further directed to a method of making the transgenic mouse.

Liljedahl et al. (1998) disclose an H2-O -/- mouse that does not express the class II MHC molecule H2-O. The mouse described in the paper is the same as the one described in the instant specification.

Thus, the claimed invention is disclosed in the prior art.

Claims 3-8 are rejected under 35 U.S.C. 102(a) as being anticipated by Altmann et al. (Immunology (December 1997) 92(1): 74).

Altmann et al. disclose an H2-Oa knockout mouse that does not express the class II MHC molecule H2-Oa. The instant claims read on the mouse described by Altmann et al.

Thus, the claimed invention is disclosed in the prior art.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to William Phillips, whose telephone number is (703) 305-3482.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER